PATENT COOPERATION TREATY

PCT

10/592919

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference ISIS0183-500	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2005/008428	International filing date *(day/month/year)* 15 March 2005 (15.03.2005)	Priority date *(day/month/year)* 15 March 2004 (15.03.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ISIS PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 19 September 2006 (19.09.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yolaine Cussac e-mail: pt11@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
PAUL K. LEGAARD
COZEN O'CONNOR
1900 MARKET STREET
PHILADELPHIA, PA 19103

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	16 FEB 2006
Applicant's or agent's file reference ISIS0183-500	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US05/08428	15 March 2005 (15.03.2005)	15 March 2004 (15.03.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(8): C12Q 1/68; C12N 15/85; A61K 48/00; C12N 15/11; CO7H 21/04 and US Cl.: 435/6, 325; 514/44, 536/23.1, 24.3, 24.5

Applicant

ISIS PHARMACEUTICALS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	23 November 2005 (23.11.2005)	Amy H. Bowman Telephone No. (571)272-0755

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/08428

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/08428

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 32

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 32 are so unclear that no meaningful opinion could be formed *(specify)*:

Claim 32 is an improper multiple dependent claim, as it recites "The method of any one of the above claims..." and claim 18 recites "The method of any one of claims 2, 3, 4, or 5..."

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/08428

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 10-16 and 23-31	YES
	Claims 1-9 and 17-22	NO
Inventive step (IS)	Claims 13 and 28	YES
	Claims 1-12, 14-27 and 29-31	NO
Industrial applicability (IA)	Claims 1-31	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-9 and 17-22 lack novelty under PCT Article 33(2) as being anticipated by Krotz et al. (US 2003/0096770 A1).

Krotz et al. teach a method of modulating the expression of a target RNA comprising administering an antisense oligonucleotide specific for the target. Krotz et al. teach an oligonucleotide that has a first region of nucleotides of one conformation, which comprises deoxynucleotides, and a second region that is 5' to the first region that comprises 2'-O-methoxyethyl groups. Additionally, the oligo comprises phosphorothioate linkages. There is a transitional moiety between the 2'-O-methoxyethyl and deoxynucleotides that incorporates a 5-methylcytosine (see ISIS-9606, page 8, for example). Additionally, the oligonucleotide has a third region of the same type as the second region that again is separated from a deoxynucleotide by a 5-methylcytosine.

Claims 10-12, 14, 15, 23-27, 29 and 30 an inventive step under PCT Article 33(3) as being obvious over Krotz et al.

Krotz et al. further teach preferred embodiments for antisense oligonucleotides comprising alkylene linkages. Krotz et al. teach that the alkenyl may be substituted or unsubstituted C1 to C10. Additionally, Krotz et al. teach that fluorinated oligos and 2' ara modified oligos are preferred (see page 6).

It would have been obvious to incorporate each of these modifications into the specific oligonucleotide discussed in the rejection above at the time the invention was made. One would have been motivated to incorporate these modifications since Krotz et al. teach that each are preferred modifications for antisense oligonucleotides to increase the binding affinity and enhance the overall activity of the oligonucleotide. One would have a reasonable expectation of success since Krotz et al. teach that these modifications enhance the activity of antisense oligonucleotides.

Claims 16 and 31 lack an inventive step under PCT Article 33(3) as being obvious over Krotz et al., as explained above, in view of Cook et al. (US 2002/0160379 A1).

Krotz et al. do not teach acyclic sugar analogs.

Cook et al. teach that acyclic sugar analogs are preferred modifications for antisense oligonucleotides and enhance the activity of antisense oligonucleotides (see page 4, for example).

It would have been obvious to incorporate an acyclic sugar analog, as taught by Cook et al., into the specific oligonucleotide discussed in the first rejection above, as taught by Krotz et al. One would have been motivated to incorporate an acyclic sugar analog since Cook et al. teach that acyclic sugar analogs are preferred modifications for antisense oligonucleotides to enhance the activity of the oligonucleotide. One would have a reasonable expectation of success since Krotz et al. teach modified antisense oligonucleotides and Cook et al. teach that acyclic sugar analogs are preferred modifications to enhance oligonucleotide activity. One would reasonably expect the modification taught by Cook et al. to benefit the oligo of Krotz et al.

Claims 1-31 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.